Trypanosomiasis

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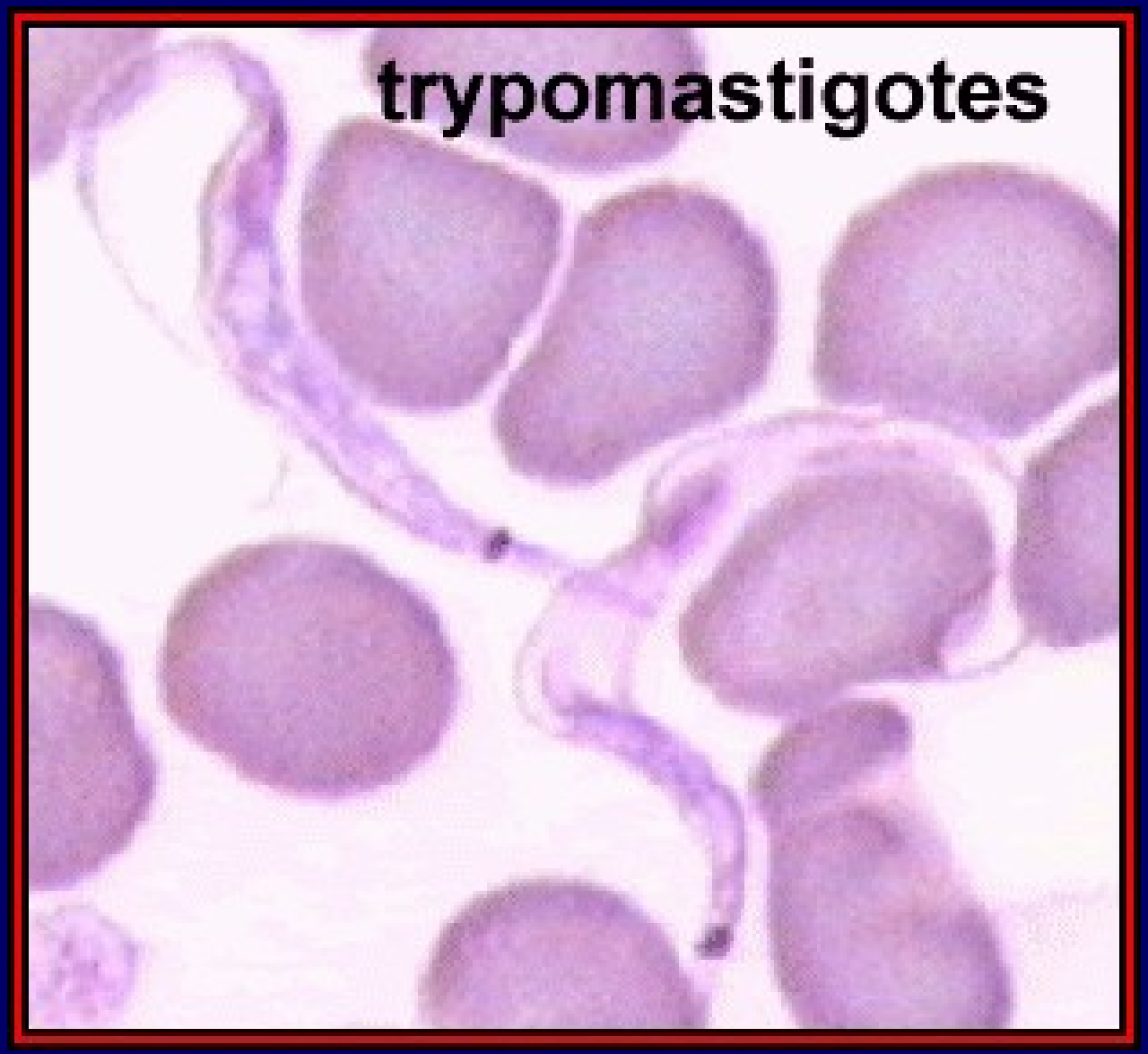
Trypanosomes

- Genus Trypanosoma
- 20 species
  - 3 pathogenic to humans
  - Others may affect domestic animals
- Flagellated protozoa
- Trypanosomiasis = zoonosis
  - Humans = “unfortunate hosts”


trypomastigotes

Trypaonsomes

- American = Chagas' disease
  - *T. cruzi*
  - Non Pathogenic
    - *T. rangelli*
- African = Sleeping Sickness
  - *T. brucei rhodesiense*
  - *T. brucei gambiense*
  - Non-pathogenic
    - *T. brucei brucei* among many others

American Trypanosomiasis

- Epidemiology
  - Southern U.S to South America
  - Most cases from Brazil
  - Highest seroprevalence: rural Bolivia (20%)
  - Classically disease of rural poor, but changing
    - Migration to cities
    - Control programs aimed at rural areas
  - Mean age = 4 years; 85% occur in <10 y.o.

Epidemiology

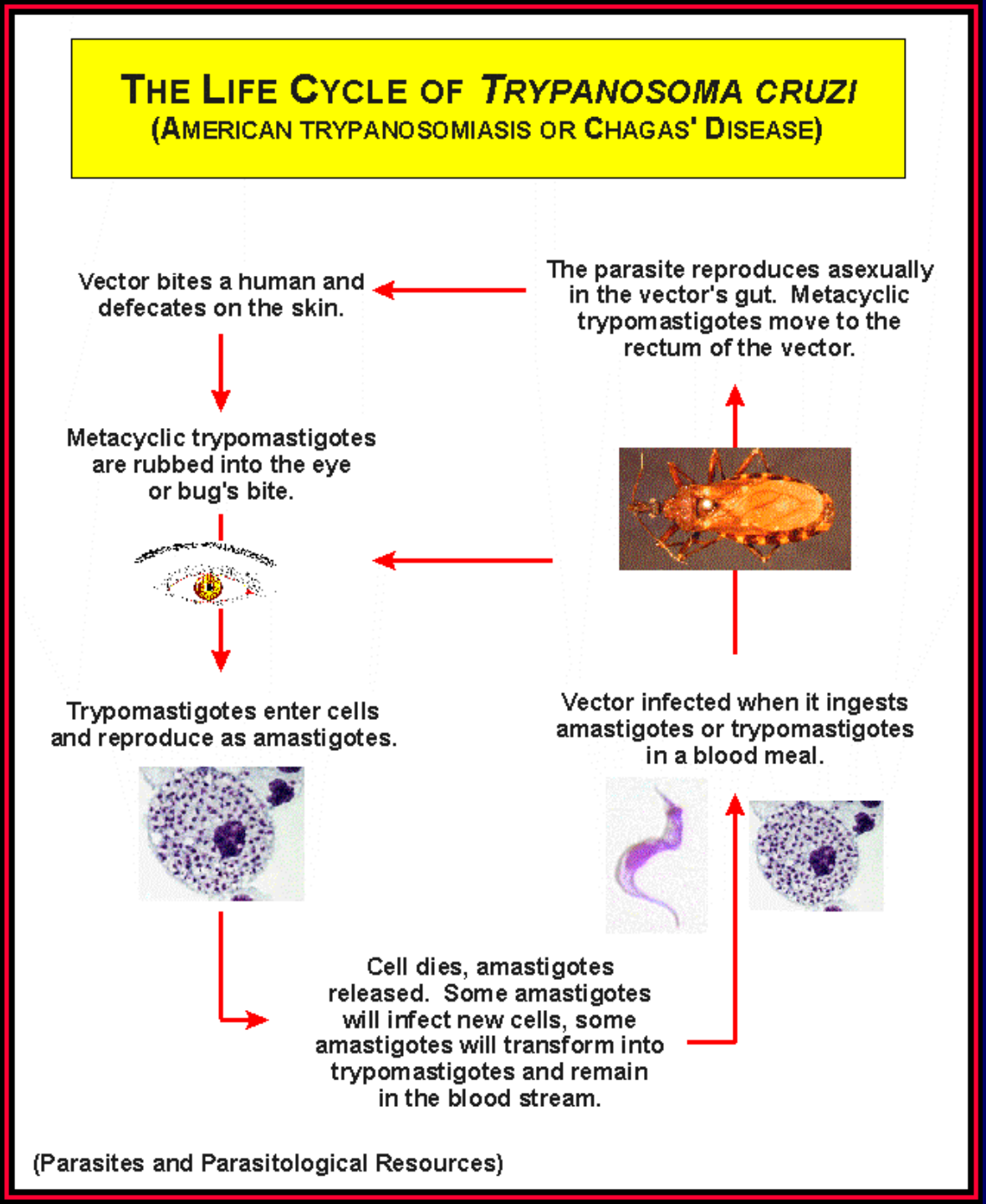
- 16-18 million seropostive Latin Americans
  - 4-5% of total population
  - Most without clinically detectable disease
- 100,000 seropositive people in US in 1990's
- Minimal risk to travelers
  - 2 case report of European traveler after 2 wk trip to Columbia

Epidemiology

- 100,000 seropositive people in US in 1990's
- Acute Chagas in US is rare
  - 4 autochthonous cases in US
    - Texas = 3
    - California = 1
  - Since 1973
    - 7 lab-acquired cases in US
    - 9 imported acute cases in US

Epidemiology

- Isolates of *T. cruzi* from S. America more pathogenic than from N. and Central America
- Brazil seems to have most pathogenic isolates
- Megasyndromes most common in:
  - Brazil, Chile, Argentina


THE LIFE CYCLE OF TRYPANOSOMA CRUZI
(AMERICAN TRYPANOSOMIASIS OR CHAGAS' DISEASE)
Vector bites a human and defecates on the skin.
The parasite reproduces asexually in the vector's gut. Metacyclic trypomastigotes move to the rectum of the vector.
Metacyclic trypomastigotes are rubbed into the eye or bug's bite.
Trypomastigotes enter cells and reproduce as amastigotes.
Vector infected when it ingests amastigotes or trypomastigotes in a blood meal.
Cell dies, amastigotes released. Some amastigotes will infect new cells, some amastigotes will transform into trypomastigotes and remain in the blood stream.
(Parasites and Parasitological Resources)

American Trypanosomiasis

www.biosci.ohio-state.edu/.../chagas_lifecycle.gif

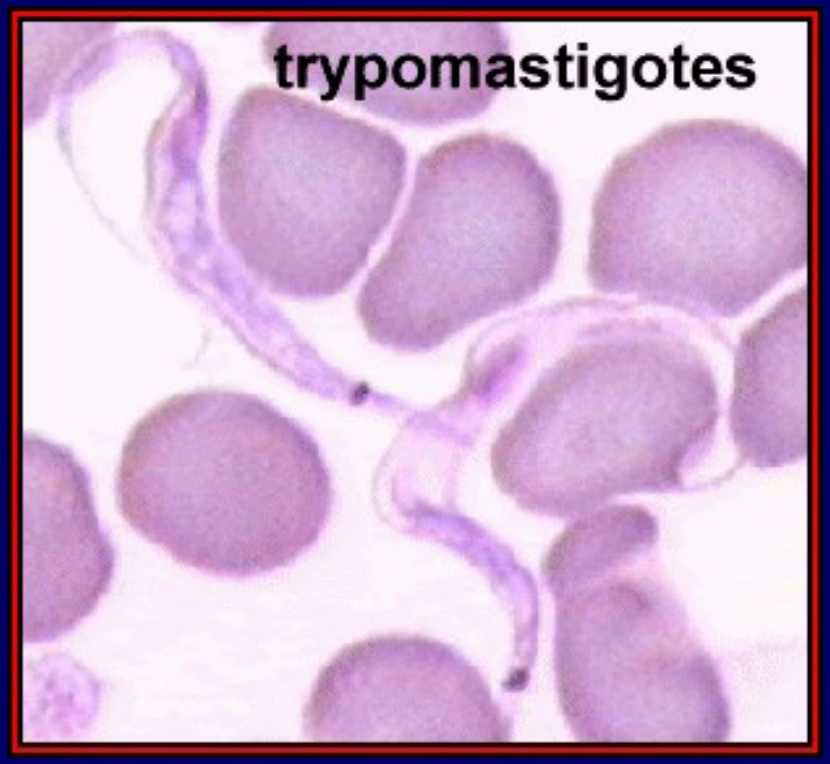
T. cruzi Stages

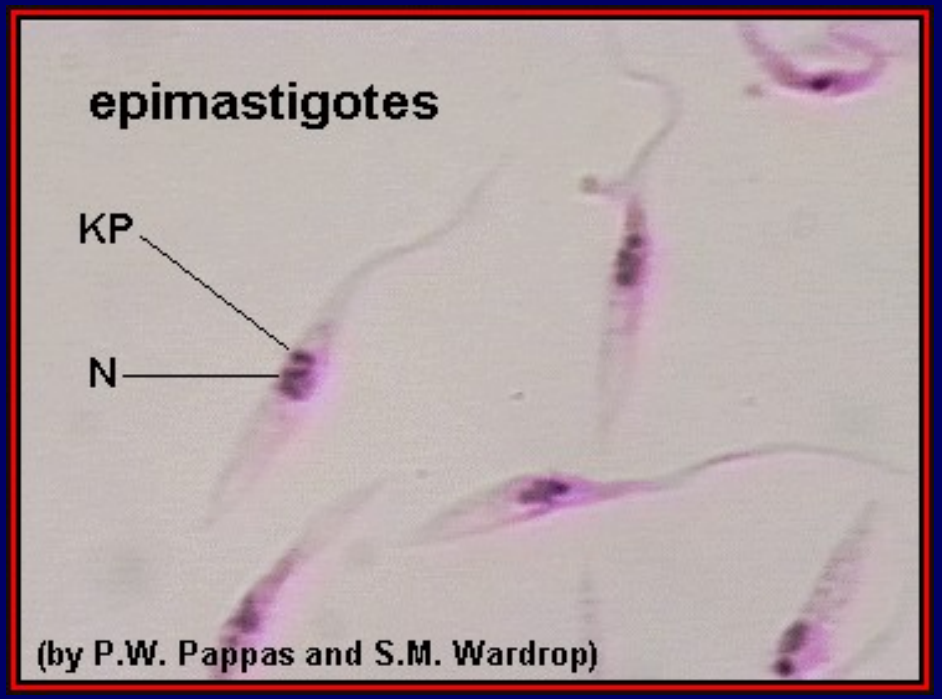
Trypomastigotes are flagellated forms in bloodstream
- -large posterior kinetoplast

Amastigotes are form found in tissue
- -oval, intracellular parasites
- -multiply by binary fission → daughters become trypomastigotes = released into host cells/circulation

Epimastigotes form from trypomastigotes inside the insect
- -anterior kinetoplast near the nucleus
- -migrate to hindgut and develop into metacyclic trypomastigotes which are concentrated in feces

Metacyclic trypomastigotes = infective form


trypomastigotes


epimastigotes
KP
N
(by P.W. Pappas and S.M. Wardrop)

American Trypanosomiasis

- Zoonosis = Animal Reservoir
  - Cycle maintained in nature with many mammals
  - Humans encroach as they farm new lands
    - Bugs become “domiciliated”
  - Domestic animals then become the reservoir in the rural community
    - Dogs, livestock (goats and sheep), fowl, guinea pigs

Adult *Rhodnius prolixus*, a kissing b

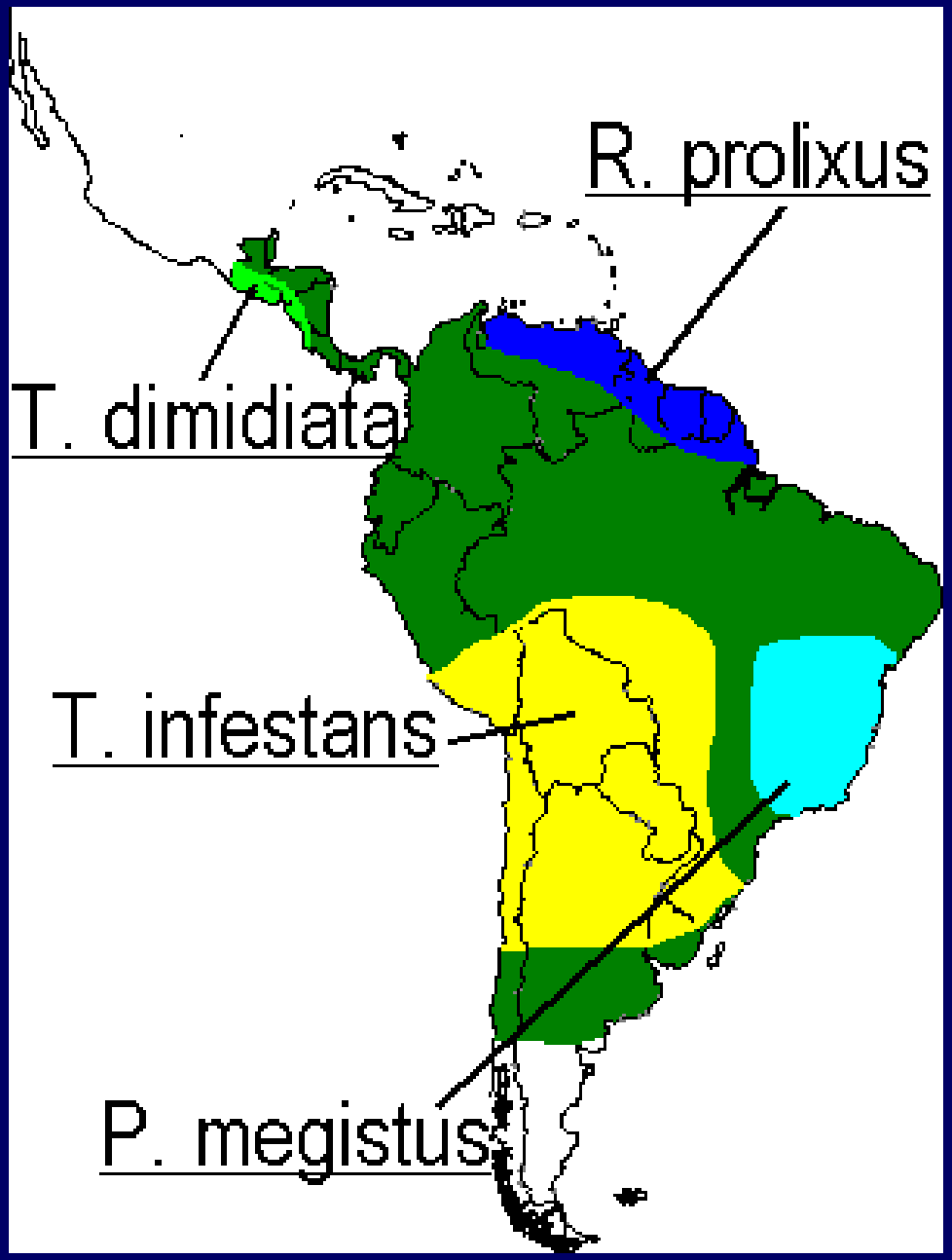
The kissing bug *Rhodnius* transmits Chagas disease to humans (Courtesy Dr. Philippe Rossignol, Oregon State University).

American Trypanosomiasis

- Vector = triatomines or reduvid bugs
  - "Kissing beetles"
  - Obligate blood feeders
    - prefer human blood
  - Live in the walls and roofs of houses and come out at night
  - CO_2 sensors help them find prey
  - Feed at least once in every stage of development and several times as adults

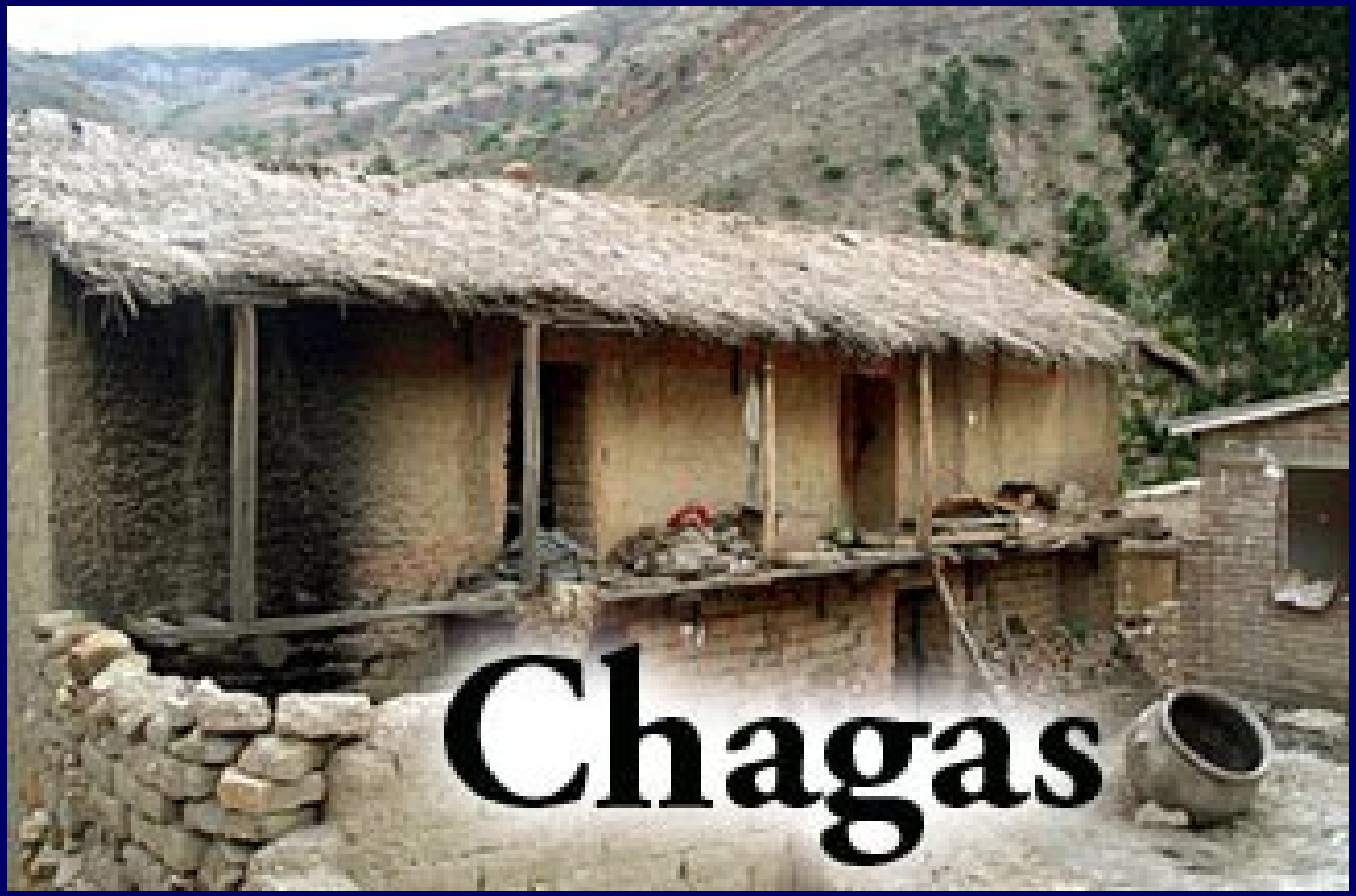
American Trypanosomiasis

- Vector = triatomines or reduvid bugs
  - Metacyclic trypomastigotes are infective in feces, which are rubbed into wound or mucosa
  - ***Triatoma infestans***
    - Adapted for housing in Central and S. America
    - Chile, Argentina, Brazil, Paraguay, Uruguay, Bolivia, Peru
  - ***Panstrongylus megistus*** – Brazil
  - ***Rhodnius prolixus*** – Venezuela, Columbia
  - ***Triatoma dimidiata*** – Ecuador
  - ***Rhodnius pallescens*** - Panama



Rare Transmission in Southern US – Why?

- Better housing
- Less encroachment on the sylvatic cycle
- Lower vector density
- Less pathogenic strains
- Defecation practices of reduvids


Chagas

American Trypanosomiasis

- Acute Illness
  - Inoculation granuloma: 50%
    - "chagoma"
    - Small papule that enlarges over 7-10 days
  - Conjunctival irritation
    - "Romana's sign"
      - Bipalpebral, unilateral, chronic edema
    - Common local lymph node enlargement

American Trypanosomiasis

- Acute Illness: Pathology
  - Rapid parasite multiplication in cyst
  - Rupture leads to release of amastigotes
  - Amastigotes found in all organs, but primarily:
    - Brain, liver, heart, GI tract

American Trypanosomiasis

- Majority are asymptomatic
- Mile Acute Illness – 10-20%
  - Mild, febrile syndrome
    - Typically low-grade
  - 7-14 days incubation period
  - Lasts 4-8 weeks

American Trypanosomiasis

- Severe Acute Illness: <5%
  - More common in young
  - Fever: high and continuous
  - Elastic, nonpitting edema (face and body)
  - Hepatosplenomegaly, lymphadenopathy
  - Anemia, lymphocytosis
  - Mildly elevated LFT’s

American Trypanosomiasis

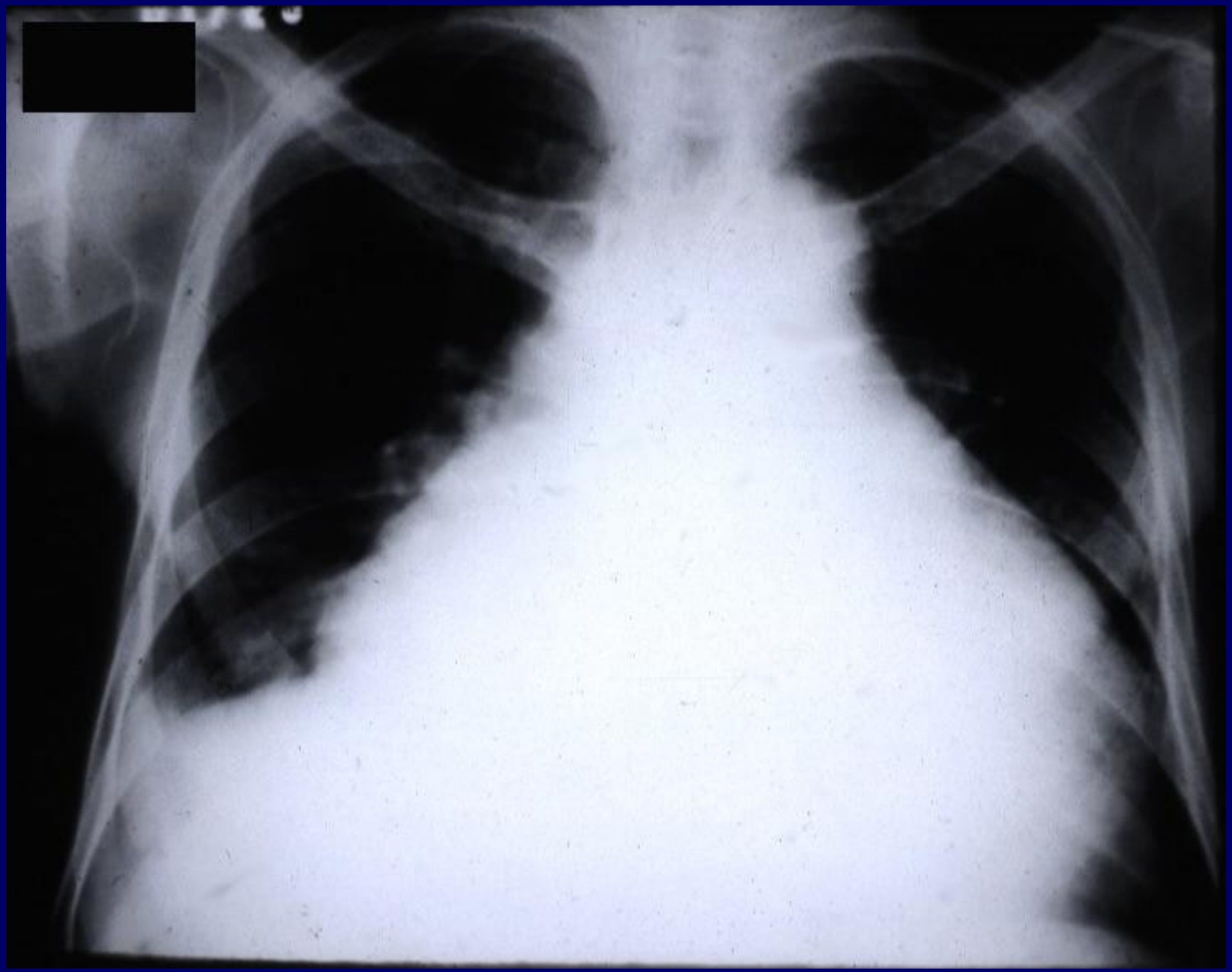
- Severe Acute Illness: <5%
- Cardiac
  - Acute heart failure, EKG changes, heart block
  - Myocarditis – extremely fulminant
    - Enlarged, dilated heart with focal hemorrhage
- Meningoencephalitis
  - Brain and meninges congested with petechiae
- Liver, spleen, lymph nodes
  - Congested and infiltrated with inflammatory cells
- Muscle layers of esophagus and GI tract affected

American Trypanosomiasis

- Indeterminate Phase
  - Amastigotes multiply in tissues indefinitely
  - Asymptomatic for the patient
  - *T. cruzi* antibody positive, low-level parasitemia
  - Organisms cleverly evade immune system
    - Shed glycoprotein to avoid complement system
    - In cells, hide from phagosomes and trypomastigotes emerge just before cell death
  - 10-30% display chronic Chagas disease decades later

Chronic Disease

- Cardiomyopathy
  - Insidious, presents 20-30 years after inoculation
  - More common in Brazil and males
  - EKG Changes: usual first sign: asymptomatic
    - PVC's, 1st degree heart block common
    - CRBBB +/- LA Hemiblock = very specific
    - Afib and LBBB are uncommon
    - Later becomes symptomatic: CHB, Stokes-Adams
  - Cardiomegaly usually apparent on CXR
  - Left Ventricular Aneurysms common
  - Emboli from intramural thrombi also seen

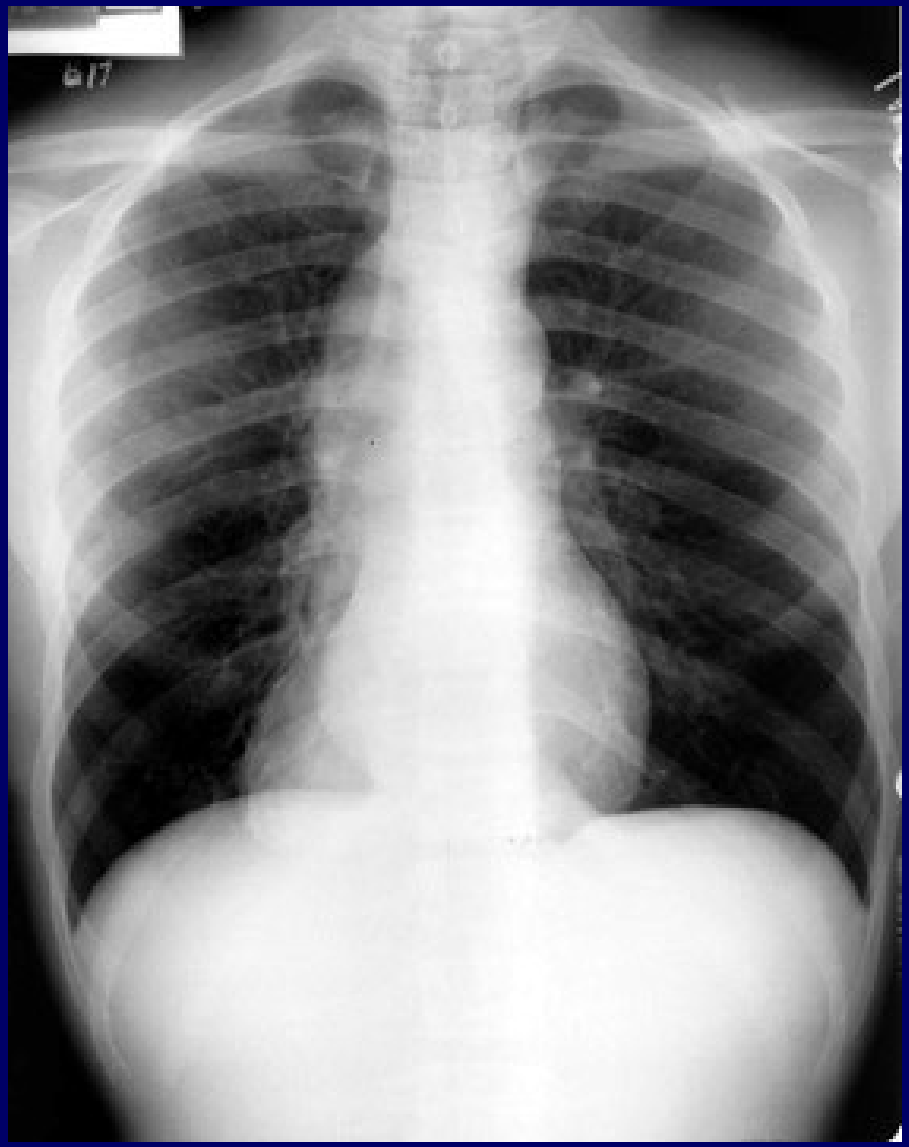


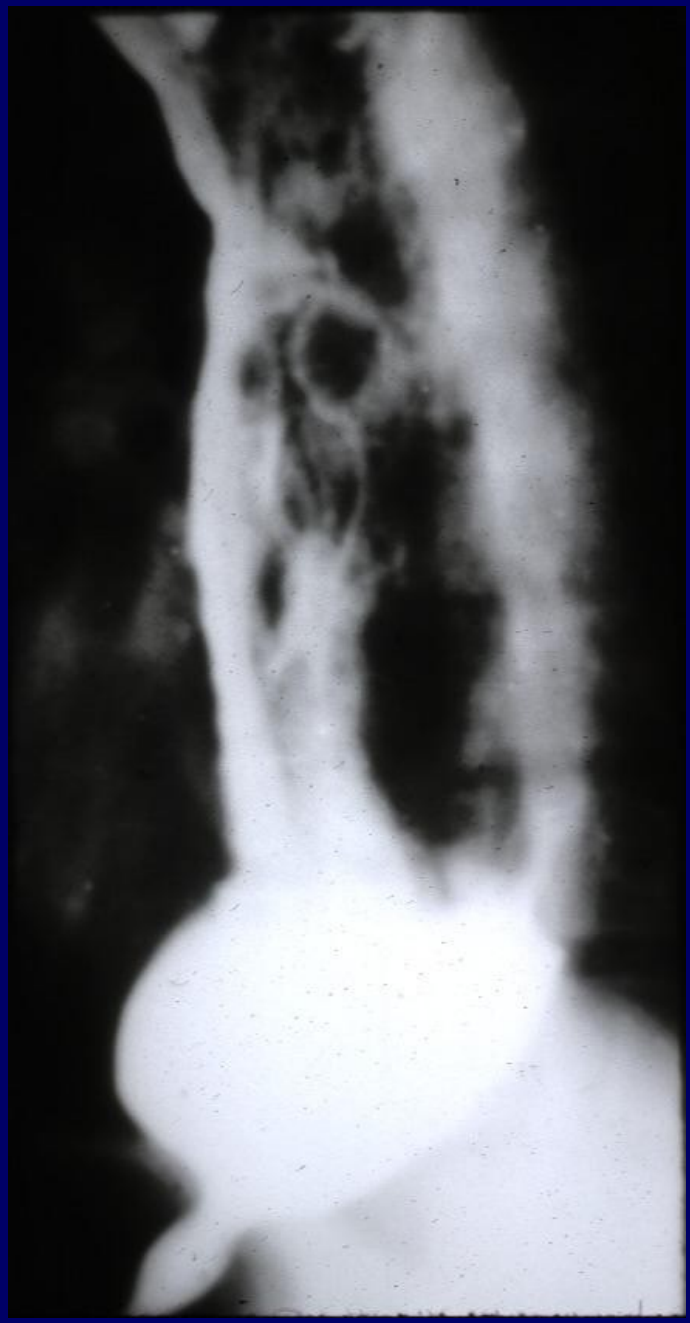
Chronic Disease

- Megasyndromes
  - Only reported south of equator
  - Brazil: 15-50% of seropositive patients
  - Few cases in Argentina and Chile
  - Destruction of submucosal parasympathetic ganglion cells = aperistalsis = retention of solids = dilation of viscous

Chronic Disease

- Megaesophagus
  - Progressive swallowing difficulty
    - Dry foods first may progress to all solids
    - Improvement of dysphagia with water is common
  - Parotid gland hypertrophy + wasting = “cat-facies”
  - Risk factor for esophageal carcinoma





Chronic Disease

- Megacolon
  - Progressive constipation, distention
  - Exam: markedly tympanic
  - Obstipation and impaction common
  - Pseudodiarrhea – liquid around solid
  - Anorexia, anemia, asthenia common
  - Complications
    - Sigmoid volvulus and “fecaloma”

American Trypanosomiasis

- Diagnosis
  - Parasitologic: Parasites in blood or tissue
    - Wet preps or Giemsa stains of blood while febrile
    - CSF, pericardial fluid, masses, BM, organ biopsies
    - Xenodiagnosis: let bugs feed and look at their feces
    - In vitro culture with biphasic media
    - Animal inoculation: takes 5-15 days
  - Use parasitologic tests for acute illness, congenital infection, transfusion illness, lab worker

American Trypanosomiasis

- Diagnosis
  - Serologic: antibodies to *T. cruzi*
    - Persist for life - IgG
    - Presumptive diagnosis for chronic infection
    - Many cross reactions: leisch, syphilis, malaria, CVD
    - US: 3 ELISA bases tests
  - Best for indeterminate or chronic disease

American Trypanosomiasis

- Treatment
  - Nifurtimox – 70% effective
    - Nitrofuran; not licensed in U.S.
    - Available through CDC via IND protocol
    - Active against trypomastigotes and amastigotes
    - Inhibits pyruvic acid synthesis: affects CHO metab
    - Big Risks: lymphomas (rabbits), polyneuropathy (usually resolves after treatment)
    - Side Effects: tremor, excitation, insomnia, anorexia, weight loss, peripheral neuritis, psychosis, hemolytic anemia with G6PD deficiency

American Trypanosomiasis

- Treatment
  - Benznidazole
    - Nitroimidazole derivative not available in U.S.
    - Works against trypomastigotes and amastigotes
    - 50% photosensitivity rashes
    - Other SE's: peripheral neuritis, anorexia, weight loss, cytopenias
    - Children tolerate better than adults

American Trypanosomiasis

- Other Treatments
  - Studied, may be useful, no recommendations:
    - Allopurinol, Itraconazole
  - Immune-modulators
    - INF-gamma – used in combination with nifurtimox or benznidazole reported
    - Potentially useful for immune compromised patients

American Trypanosomiasis

- Nifurtimox
  - Adults: 8-10 mg/kg/day divided q8, after meals
  - Children: 15mg/kg/day divided q8, after meals
  - Course varies: 30 to 120 days
- Benznidazole
  - All: 5-10mg/kg daily divided q12
  - 30-60 day course

American Trypanosomiasis

- Who to treat?
  - Acute, congenital, laboratory accidents: definitely
  - Indeterminate: controversial
    - Some models implicate ongoing infection as primary determinant of cardiac destruction
  - Chronic: usually supportive as it is often too late and toxicity may outweigh benefit

American Trypanosomiasis

- Supportive Therapy
  - Cardiac
    - Follow with EKG's every 6 months
    - Antiarrhythmics, but NOT beta-blockers
    - Pacers if walls aren't too thin
    - Thromboembolic prophylaxis
    - Transplantation: not recommended due to risk of recurrence

American Trypanosomiasis

- Supportive Therapy
  - Megaesophagus
    - goal = relief of functional obstruction at LES
    - Balloon dilation of LES, Heller's procedure (extramucosal cardiomyotomy), total esophagectomy with intestinal replacement, botox
    - Surveillance for esophageal carcinoma
  - Megacolon
    - Mild: dietary fiber + stool softeners, regular use of laxatives/enemas
    - Severe: resection

American Trypanosomiasis

- Outcomes
  - <5% mortality in acute phase
  - 70-90% exposed never develop chronic disease
  - 25% eventually have EKG abnormalities
  - 1% megasyndromes at 20-50 years old
  - Predictors of death:
    - <50% 4 year survival if: CHF, global LV dysfct, apical LV aneurysm at presentation

Uncommon Transmission

- Transfusions
  - Big problem in endemic areas
  - 13-23% risk for every infected unit
  - Controls in place
    - Education and screening
      - Questionanaires, serology
    - Parasite inactivation
  - Rare, but reported in US
    - 5% of Salvadoran and Nicaraguan immigrants in DC area
    - May increase as immigration increases

Uncommon Transmission

- Congenital
  - 1-10% of deliveries of women with chronic infections
    - Spontaneous abortion, prematurity, IUGR
  - Breast feeding may be more common route
  - Prompt diagnosis desired b/c can treat infants
    - Moms are asymptomatic so many countries screen
    - Cannot use serologic tests on infant - crossover

Uncommon Transmission

- Person-Person
  - Case reports of transplant organ transmission
- Ingestion
  - Hunting dogs in US
  - Contaminated food outbreaks
  - Humans eating bugs
- Occupational
  - >50 lab worker cases – pipetting by mouth usual route

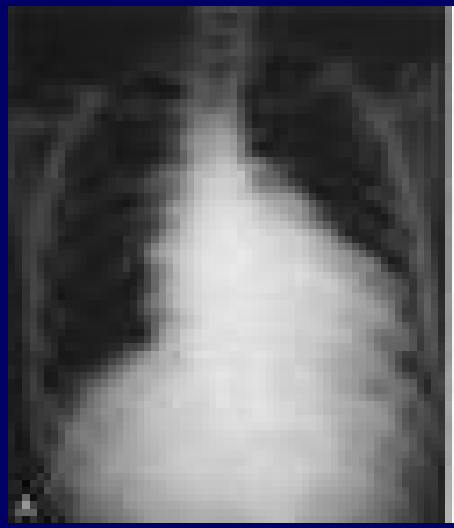
American Trypanosomiasis

- Disease Control
  - Bug spray on walls
  - Brick rather than “thatched-roofed” or mud huts
  - Cultural teaching
  - Night-lights (bugs prefer dark)
  - Banning animals from house
  - National and multinational programs
  - Screening blood donor pool or at least treating blood with gentian violet to kill organisms if not possible
  - Congenital: mothers avoid nursing until treated

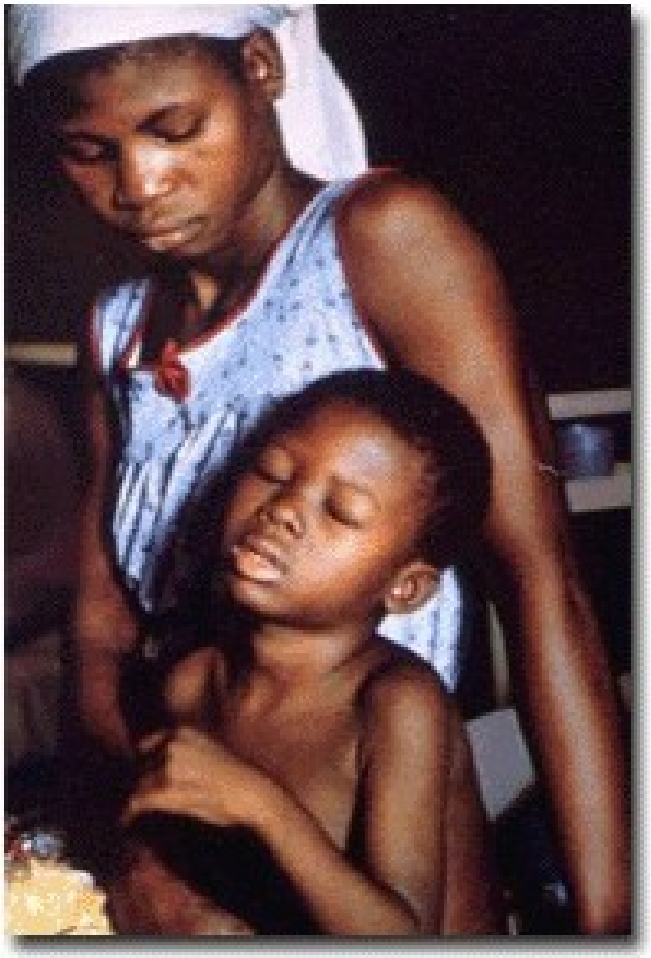
American Trypanosomiasis

- Mission Impact
  - Disease of rural poor but becoming disease in cities as populations migrate
  - Opportunity for Humanitarian and Aid Missions to this region
    - Education
    - Treatment
    - Disease control
  - Potential threat to long-term deployments

Chagas' Disease (Trypanosoma cruzi)

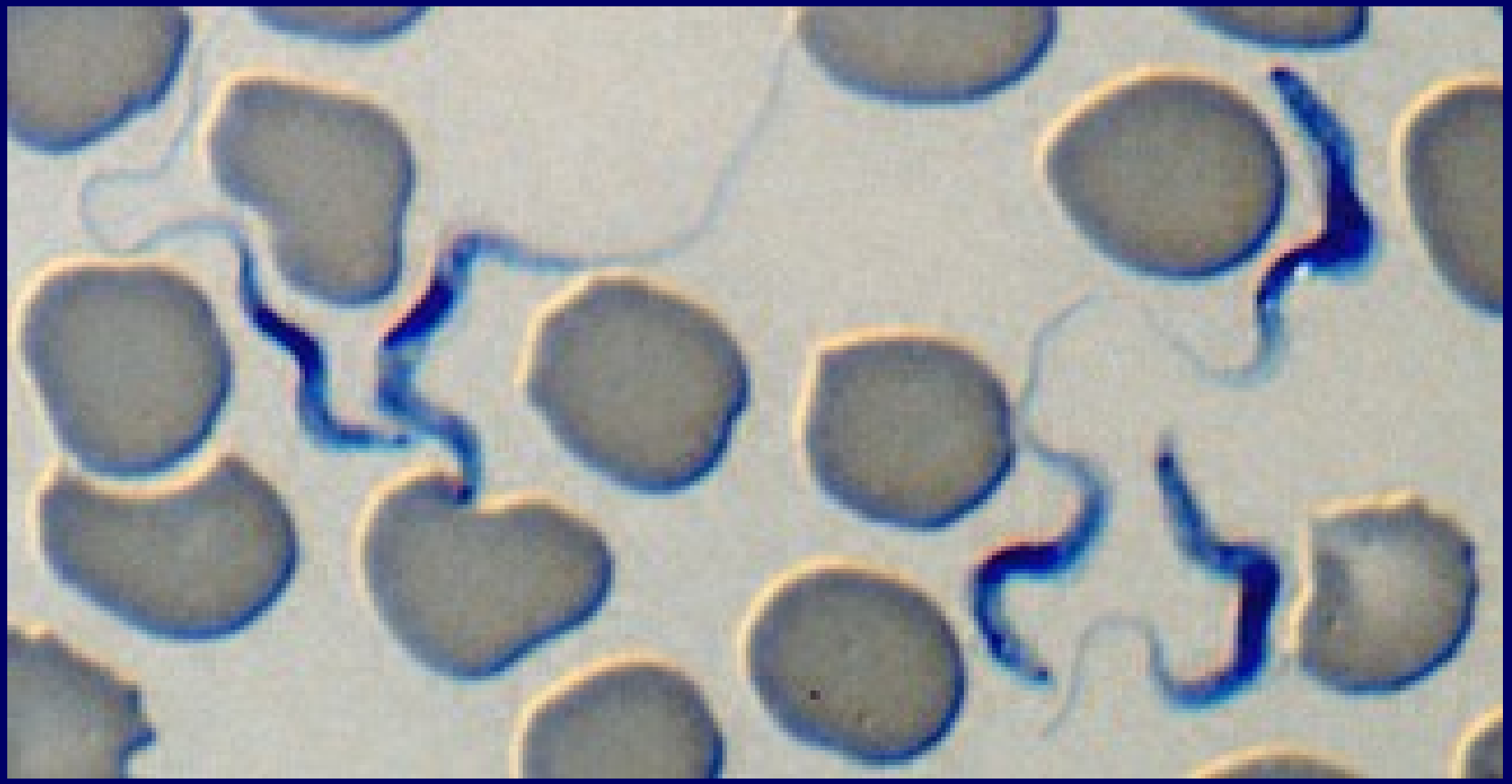


African Sleeping Sickness (Trypanosoma brucei)



African Trypanosomiasis

- African = Sleeping Sickness
  - *T. brucei rhodesiense* = E. African HAT
  - *T. brucei gambiense* = W. African HAT
  - Non-pathogenic
    - *T. brucei brucei* among many others
    - David Bruce who described nagana in cattle
- Human African Trypanosomiasis = HAT

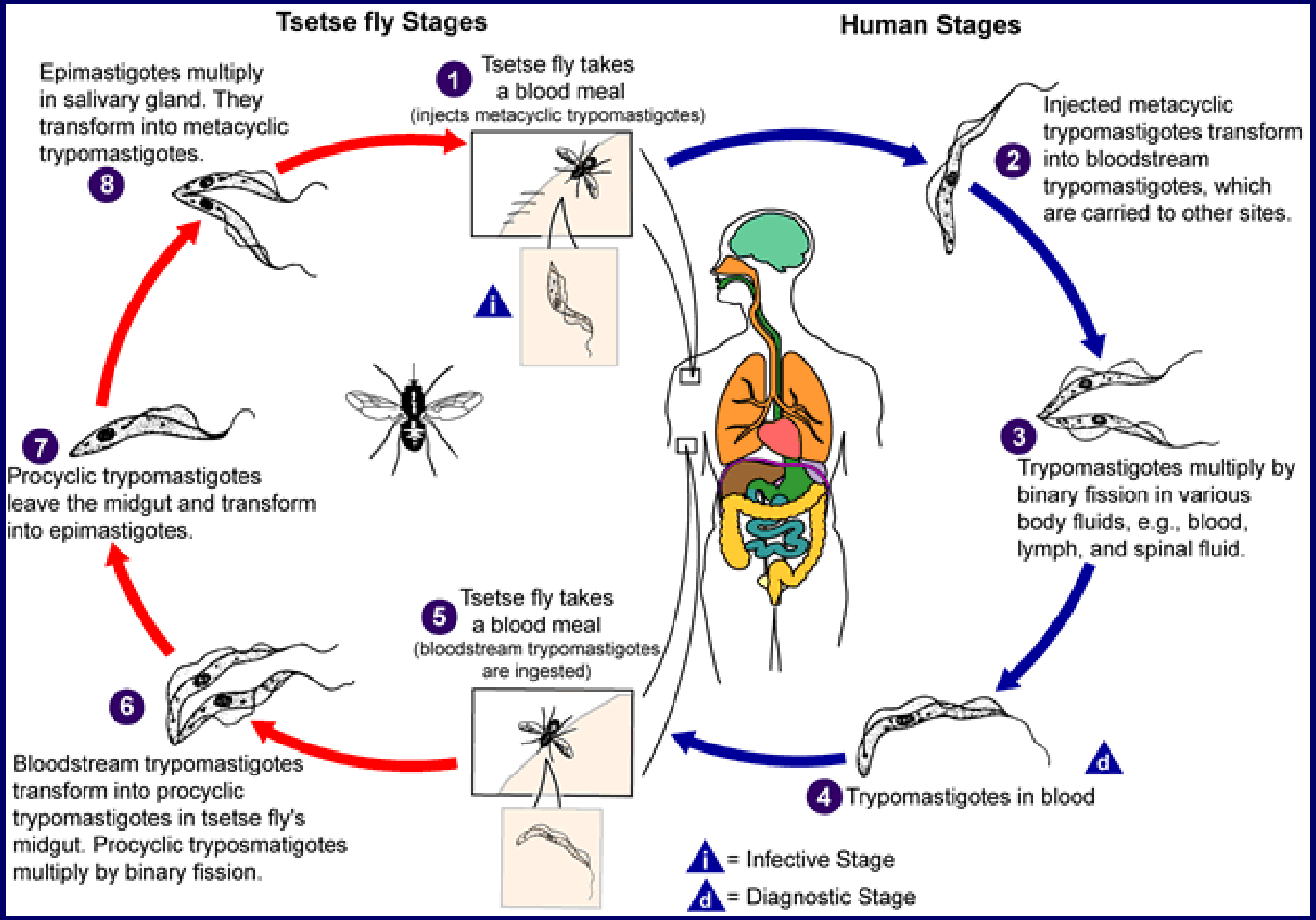


African Trypanosomiasis

- African versus American Trypanosomiasis
  - Vector
    - Tsetse flies, not reduvids
  - No intracellular form
    - Trypomastigotes circulate in blood stream of humans or other mammals

African Trypanosomiasis

- Tsetse flies: genus *Glossina*
  - Bloodsuckers – bites are painful
  - Wide range: rain forest to savannas


Tsetse fly Stages
Human Stages
Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.
8
1 Tsetse fly takes a blood meal
(injects metacyclic trypomastigotes)
i
2 Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other sites.
3 Trypomastigotes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
d
4 Trypomastigotes in blood
5 Tsetse fly takes a blood meal
(bloodstream trypomastigotes are ingested)
6 Bloodstream trypomastigotes transform into procyclic trypomastigotes in tsetse fly's midgut. Procyclic tryposmatigotes multiply by binary fission.
7 Procyclic trypomastigotes leave the midgut and transform into epimastigotes.
i = Infective Stage
d = Diagnostic Stage

Epidemiology

- >50 million at risk
- Gambian: 1993 survey
  - 55,000 deaths
  - 1.78 million disability-adjusted life-years lost
  - Congo = 19,340 cases in 1994
  - Cases may be grossly underestimated
    - Poverty, political instability
  - Angloa, Sudan = epi impossible b/c of war
- Rhodesian: much more controlled
  - Small foci in Kenya, Mozambique, Zambia, Tanzania, Malawi

Tunisia
Morocco
Western Sahara
Algeria
Libya
Egypt
Cape Verde
Mauritania
Mali
Niger
Chad
Sudan
Eritrea
Djibouti
Gambia
Sierra Leone
Guinea Bissau
Liberia
Côte d'Ivoire
Togo
Ethiopia
Somalia
Equatorial Guinea
Gabon
Kenya
Sao Tome and Principe
Angola
Malawi
Zimbabwe
Madagascar
Namibia
Botswana
Mozambique
Swaziland
Lesotho
South Africa
West African trypanosomiasis
East African trypanosomiasis

T. b. gambiense (W. HAT)

- Long incubation before disease
  - Asymptomatic with high parasitemia
  - Estimated to last months to years
  - Facilitates spread

T. b. gambiense (W. HAT)

- Stage 1: Hemolymphatic
  - Tryps in blood or LN aspirates; none in CSF
  - Headaches, myalgias, malaise, fatigue
  - Cyclic fevers relating to parasitemia
  - Cervical LAD common
    - Winterbottom's sign = Post Cervical LAD-85%
  - 10-20% splenomegaly
  - Pruritis and transient edema

T. b. gambiense (W. HAT)

- Stage II: Meningoencephalitic
  - Parasites rare in blood – low infx risk
  - Constant, severe headaches
  - Progressive somnolence with nocturnal insomnia
  - Stop taking PO, stop talking, coma
  - Extrapyramidal, Parkinsonian signs can occur
  - Psychosis uncommon but should r/o HAT
  - Universally fatal if untreated – months to years

T. b. rhodesiense (E. HAT)

- More acute than Western HAT
- Similar stages but weeks, not months
  - Fever and parasitemia 1-3 weeks after bite
    - LAD less common
  - CNS disease same but fatal in 1-3 months
- More of a risk to traveler's than W. HAT, particularly in big game parks

Inoculation Chancre

- Indurated, painful chancre after bite
- Uncommon in Africans – more in visitors
- More common in E. than W. HAT
- Occurs 1-2 weeks after bite
- Disappears spontaneously over 1-3 weeks

Diagnosis

- Parasite assays
  - LN aspirate – examine for motile tryps
  - Blood smear
    - Immediate and after Giemsa stain (for malaria)
  - Wet prep of inoculation chancre
- CSF
  - Diagnosis if CNS symptoms present
  - To stage if parasites found in blood
  - Parasites increase with leukocytosis

Diagnosis

- CATT
  - Card Agglutination Test for Trypanosomiasis
  - Only currently used serologic assay
  - Field use, no electricity, 10 minute results
  - 96% sensitive, but less specific
  - 66-89% PPV in selected hospital patients
  - Much less PPV in field with a 1-10% incidence
  - Used for *T. b. gambiense* only

African Trypanosomiasis

- Treatment
  - *T. b. rhodesiense* is more resistant of two
  - Distinguish primarily by geographic location
  - CNS disease warrants different therapy
    - LP must be performed on all patients, even in absence of symptoms
    - CNS disease defined as: evidence of trypanosomes or pleocytosis >5 cells/mm^3

African Trypanosomiasis

- Non-CNS Treatment: *T. b. gambiense*
  - Pentamidine
    - Aromatic diamidine approved in US but not for this
    - 4mg/kg daily X 7 days IV or IM = 93% cure rates
    - Adverse events: sterile abscesses at injection site, hypocalcemia, hyperkalemia, renal failure, neutropenia, arrhythmias, hypoglycemia, post-therapy diabetes
    - 1% die on therapy for unclear reasons
    - Suramin less effective; melarsoprol too toxic

African Trypanosomiasis

- CNS Treatment: *T. b. gambiense*
  - Eflornithine
    - inhibits ornithine decarboxylase
  - Equal to melarsoprol and less toxic
  - Expense is limiting factor for use, huge volumes another
  - 100mg/kg IV q6 X 14 days
    - 90% cure of late disease, 98% cure of relapses
    - 2% die on therapy
  - SE's: cytopenias from BM toxicity in >50%

African Trypanosomiasis

CNS Treatment: *T. b. gambiense*

- Melarsoprol
  - Toxic, but cheap, and commonly used
  - Trivalent arsenical with 94-97% cure rates
  - 4-6% death rate
  - <1% penetrates CSF, but works b/c so effective
  - No evidence of resistance despite years of use
  - 3.6mg/kg (max 180 mg) IV daily X 3, repeat in 1 week, again in 2 weeks if CSF cell counts >20.
  - SE's: reactive encephalopathy serious in 4-8%, polyneuropathy (10%)

African Trypanosomiasis

- Non-CNS Treatment: *T. b. rhodesiense*
  - Suramin considered better than pentamidine
  - Failure rate variable: 0-31%
  - 200mg test dose recommended b/c of uncommon anaphylaxis at 1/20,000
  - 20mg/kg IV (max 1.5g) days 1, 3, 6, 14, 21
  - SE's: fever, proteinuria, paresthesias, urticaria
  - Poor CSF penetration precludes CNS use

African Trypanosomiasis

- CNS Treatment: *T. b. rhodesiense*
  - Melarsoprol cures 95%
  - Encephalopathy occurs in 5-18%; Mortality in 3-12% on therapy
    - Both higher than with *T. b. gambiense*
  - Complicated incremental WHO dosing schedule where small doses are increased gradually – no comparative trials

African Trypanosomiasis

- Control
  - Half-yearly screening for cervical LAD
    - Fell apart after colonial period
  - Case-finding CATT teams
  - Vector targeting
    - Tsetse fly trapping
      - Need to maintain b/c of long incubation period
    - Sterilizing tsetse flies
  - Travelers
    - No prophylaxis b/c rare; but insect precautions always

African Trypanosomiasis

- Mission Impact
  - Disease of rural poor
  - Opportunity for Humanitarian and Aid Missions
    - Education
    - Treatment
    - Disease control
  - “Opportunistic Infection” of political destabilization

African Trypanosomiasis

	Gambian	Rhodesian
Agent	***T. b. gambiense***	***T. b. rhodesiense***
Vector	**Riverine Tsetse (*G. palpalis* gp.)**	**Savanna Tsetse (*G. morsitans*)**
Distribution	**West and Central Africa**	**Eastern and Southern Africa**
High-Incidence Countries	**The Congo, Angola, Sudan, Uganda, Congo-Brazaville**	**Uganda, Tanzania, Mozambique, Zambia**

African Trypanosomiasis. Hunter's Tropical Medicine. WB Saunders Company, 2000; 644

African Trypanosomiasis

	Gambian	Rhodesian
Location	**Rivers, watering holes**	**Cleared bush, savannas**
Reservoir	**Humans**	**Antelope, cattle**
Disease	**Chronic**	**Acute**
CNS Invasion	**Late**	**Early**
Duration	**Months to years**	**Weeks to months**

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African Trypanosomiasis

	Gambian	Rhodesian
Parasitemia	**Low**	**High**
Diagnosis	**Aspirate lymph node, CSF examination**	**Peripheral blood or CSF examination**
Serology	**Card Agglutination Test for Tryp.**	**None**
Control	**Active case finding**	**Tsetse trapping**

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African Sleeping Sickness (Trypanosoma brucei)